Peer Review File

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Comment 1. Generally, the kidney is hyperechogenic in the neonatal period. What is the definition of "hyperechogenicity" in this study? The authors should present the photograph of the ultrasonography in patients. If possible, please compare the echogenicity between the patients with 17q12 microdeletion and healthy control.

Reply 1. As recommended, the definition of "parenchymal kidney hyperechogenicity" was added and referenced in the "Methods" section- page 5 Lines 109-111 (highlighted). We also added a set of figures (new Figures 1 and 2) to illustrate the dynamics of improving kidney hyperechogenicity with age in Patients 1 and 6.

Comment 2. On the description of Methods, please describe the microarray analysis method in more detail. Which company's kits did you use?

Reply 2. We added a detailed description of molecular genetic methods in the "Methods" section,Page 5 Lines 101-107, as requested: "Chromosomal microarray analysis (CMA) was performed using DNA extracted from amniotic fluid or blood. CMA was performed with the CytoScan 750K array (Affymetrix, Santa Clara, CA), which is composed of 550,000 nonpolymorphic copy number variant probes and more than 200,000 single-nucleotide polymorphism probes, with an average resolution of 100 Kb. Analysis was performed with ChAS software from Affymetrix. Genomic coordinates were evaluated in accordance with genome build GRCh37/hg19. Analyses were according to the standards and guidelines of the American College of Genetics and Genomics for constitutional cytogenomic microarray analysis".

Comment 3. On page 11 Line 261, the authors described "Our finding is also consistent with reports of a very low rate of progression to end-stage renal disease during childhood as well as thereafter 12.8%???". What is the last three question mark?

Reply 3. This was a regrettable typo which was corrected.

Comment 4. On page 12 Line 268, the authors described "Another novel finding among our patients is the coexistence of both types of HNF1B-associated kidney abnormalities, i.e., cystic kidneys and CAKUT, which presented sequentially in Patient 3. Coexistence of these 2 features of HNF1B-associated kidney involvement had been reported only once in a post-mortem study of aborted fetuses." I think this is not surprising because the co-exitance of renal cysts and CAKUT has already been reported in other reports (Okorn C, et al. Pediatr Nephrol 2019; 34: 1065-1075, Nagano C, et al. Clin Exp Nephrol 2019; 23: 1119-1129, and so on).

Reply 4. Many thanks for providing us with these two important HNF1B mutation/ deletion cohorts which we now included and referred to in the "Discussion", Pages 12-13 Lines 286-292: “The great majority of HNF1b mutation cohorts, including the most recently reported ones, described the renal cystic/dysplastic changes as the most prominent imaging feature of this mutation. While HNF1B mutation is recognized as one of the most commonly identified genetic causes of CAKUT, the simultaneous occurrence of these two expressions of the same mutation was very rarely reported: specifically once in a post-mortem study of aborted fetuses (18) and in 2 cases among two recently reported cohorts of 67 (27) and 33 (28) patients carrying the mutation", and the appropriate references were now included.
We would like to emphasize that the great majority of patients described in these studies had mostly sonographic cystic/dysplastic changes. Thre was only one case of tubulointerstitial involvement - not clearly defined by the authors in the cohort - out of 62 HNF1B mutation/deletion cases described by Okorn et al (28), and only 1 patient out of the 33-patient cohort reported by Nagano et al(27) had VUR diagnosis, with 2 others reported to have some hydronephrosis without a clearcut CAKUT diagnosis. We mention the delayed diagnosis of CAKUT and secondary UTI after the initial cystic renal disease features of HNF1B had triggered the genetic diagnosis. Our aim was to highlight the importance of alertness to these features of HNF1B mutation/deletion diagnosis during the patients' follow-up and their clinical consequence.

Comment 5. On page 12 Line 276, the authors described “Neurodevelopmental involvement is one of the most feared extrarenal features of a HNF1B mutation”. I think this is incorrect because the patients with HNF1B “point” mutation such as missense, nonsense, splice site mutation do not generally show neurodevelopmental disorder although 17q12 deletion syndrome including HNF1B and LHX1 showed developmental delay.
Reply 5. Indeed patients with HNF1B point mutations were not reported to have an increased rate of autistic spectrum disorder or other neurological or developmental abnormalities in contrast to those with the HNF1B deletion type of mutation. We corrected our statement in the text accordingly:” HNF1B deletion”, with thanks.

Comment 6. On page 13 Line 298, “congenital abnormalities of the kidney and urinary tract” should be replaced with “CAKUT”.
Reply 6. Done, as advised.